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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/835,482	04/08/1997	ALAN A. RUBIN	7483/73068	5100

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EXAMINER
SHEIKH, HUMERA N

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 12/15/2003

42

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/835,482	RUBIN, ALAN A.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communicati n appears n the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Receipt of the Amendment filed 08/15/03 and the Letter and Fee notice filed 11/07/03 is acknowledged.

The 35 U.S.C. 112 second paragraph rejections have been *withdrawn.*

Claims 24-31 are pending. Claims 1, 11, 12, 17, 18 and 21-23 have been cancelled as requested. New claims 24-31 have been added by virtue of the amendment. Claims 24-31 are rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 24-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dempski *et al.* (US Pat. No. 4,900,755) in view of Conte *et al.* (US Pat. No.5,738,874).

Dempski teaches an oral controlled release formulation comprising a combination of carbidopa and levodopa useful for the treatment of Parkinson's disease whereby treatment of parkinsonism with the controlled release formulation provides several advantages over treatment with the standard carbidopa/levodopa combinations previously employed (see Abstract and col. 1, lines 1-60). Dempski teaches that the controlled release tablet of carbidopa/levodopa of the invention is a matrix or monolithic drug delivery system containing carbidopa and levodopa as the active ingredients. The system consists of the two drugs, uniformly dispersed in a polymer vehicle at a concentration that is greater than either drug solubility in the polymer vehicle which is either a single or a combination of polymers. The art recognizes the importance of treating Parkinson's disease with a dosage form which prevents the emergence of "wearing-off" and"on-off" phenomena. The combination of carbidopa and levodopa in a controlled release preparation can help to prevent the emergence of "wearing-off" and "on-off" phenomena and the combination of carbidopa and levodopa was designed to obviate or at least alleviate problems associated with standard combination therapy (see col. 1, line 44 through col. 2, line 52).

With regards to the concentration of the drugs, Dempski teaches overlapping ranges at col. 3, lines 45-60. For instance, in a typical formulation, levodopa can be in the range of 20-200 mg, and more preferably in a range of 100-400 mg. Carbidopa can be contained in the range of 5-300 mg, more preferably, 25-100 mg. These ranges read on the applicant's claimed ranges. Furthermore, it is deemed obvious to one of ordinary skill in the art that suitable ranges could be determined through routine or manipulative experimentation.

Specific examples (1-7) of the carbidopa/levodopa formulation are demonstrated at col. 3, line 45 through col.5, line 60.

Dempski teaches a single-layered tablet form (controlled release layer) and is deficient only in the sense that he does not teach a two-layered or bi-layered tablet dosage form that comprises an immediate release layer and a sustained release layer.

Conte teaches a pharmaceutical tablet capable of liberating one or more drugs at different release rates wherein the tablet consists of a first layer containing one or more drugs with immediate or controlled release formulation and a second layer containing one or more drugs, either equal to or different from those of the first layer, with a slow release formulation (see abstract). An optional barrier-type coating layer can be placed between the first and second layers. Conte also teaches various drugs, which can be present in the formulation, including both carbidopa and levodopa, and teaches combination therapy with both carbidopa and levodopa in a formulation with multiple release profiles (see cols. 2 and 3 and claim 6).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Conte within the teachings of Dempski because Conte teaches a bi-layered pharmaceutical tablet comprising various drugs (i.e., carbidopa, levodopa) wherein the first layer contains one or more drugs with immediate or controlled release formulation and a second layer containing one or more drugs with slow release formulation and similarly Dempski teaches an oral controlled release formulation comprising a combination of carbidopa and levodopa useful for the treatment of Parkinson's disease. The expected result would be an improved two-layered pharmaceutical dosage form for the effective treatment of Parkinson's disease, as similarly desired by the applicant.

Response to Arguments

Applicant's arguments filed 08/15/03 have been fully considered but they are not persuasive.

Firstly, the applicant argued, "Dempski's formulation was flawed by a serious 2-hour delay in the onset of action of carbidopa-levodopa. Moreover, Dempski teaches a single layered tablet, a sustained release profile and excipients which support that profile whereas the present invention teaches a bilayer tablet comprising excipients which support an immediate and sustained release pattern."

These arguments have been carefully considered, but were not found to be persuasive. Dempski teaches an oral controlled release formulation comprising a combination of carbidopa and levodopa useful for the treatment of Parkinson's disease whereby treatment of parkinsonism with the controlled release formulation provides several advantages over treatment with the standard carbidopa/levodopa combinations previously employed. The art recognizes the importance of treating Parkinson's disease with a dosage form that prevents the emergence of "wearing-off" and "on-off" phenomena. Dempski, as discussed above, teaches the claimed combination of carbidopa and levodopa and acknowledges the advantages of employing the carbidopa/levodopa combinations. The applicant's argument that Dempski teaches a single layered tablet, a sustained release profile and excipients which support that profile is not persuasive since Dempski teaches the claimed drug combination. Dempski teaches a single layered tablet. The secondary reference of Conte was relied upon for the generic teaching that it is known to formulate bilayered tablets of carbidopa/levodopa combinations, as similarly desired by the applicant. Thus the prior art teaches a similar formulation comprising the same ingredients for a similar field of endeavor as instantly being claimed.

Secondly, the applicant argued, "Conte's tablet formulations contain immediate and sustained release characteristics, but their arrangement and symmetry, their composition, construction are significantly different from those elements of the present invention. Conte claims a 3-layer tablet consisting of a first layer containing immediate or controlled release drugs, a second layer containing one or more drugs either equal to

or different from the first layer with slow release formulation and a third rate-controlling barrier layer containing drug if necessary. The present invention teaches a 2-layer tablet comprising a sustained release core overcoated only with an immediate release layer. In addition to bilayer tablets, the multilayer tablets of the present invention contain an excipient layer, which unlike Conte's third barrier layer, is drug-free and does not contain rate-controlling polymers. Conte claims a tablet consisting of three discrete disc-shaped layers arranged adjacent to one another. Drug release characteristics are a function of exposure of each layer to an aqueous medium and are controlled, in part, by limited aqueous access imposed by the physical structure of the 3-layered tablet. Bilayer tablets of the present invention, on the other hand, consist of a core drug component overcoated by a drug layer which has total external surface exposure and exclusive availability for an initial rapid burst of therapeutic action."

These arguments have been thoroughly considered, but were not found to be persuasive. Conte, as delineated above, teaches a pharmaceutical tablet capable of liberating one or more drugs at different release rates wherein the tablet consists of a first layer containing one or more drugs with immediate or controlled release formulation and a second layer containing one or more drugs, either equal to or different from those of the first layer, with a slow release formulation (see abstract). A barrier-type coating layer can be placed between the first and second layers. Conte teaches various drugs, including both carbidopa and levodopa, and teaches combination therapy with both carbidopa and levodopa in a formulation with multiple release profiles. The applicant's argument that Conte claims a 3-layer tablet consisting of a first layer containing

immediate or controlled release drugs, a second layer containing one or more drugs either equal to or different from the first layer with slow release formulation and a third rate-controlling barrier layer containing drug if necessary versus the present invention, which teaches a 2-layer tablet comprising a sustained release core overcoated only with an immediate release layer is not persuasive since Conte does teach a multi-layered tablet comprising an immediate release layer adjacent to or positioned below the sustained release layer. Conte, at column 5, lines 53-63 teaches that the tablets offer the advantage of releasing the drug(s) according to a prefixed schedule; therefore lower amounts of drug can be administered. Additionally, the tablets find very important therapeutic applications, e.g., when one or more drugs are to be administered at different times and when one drug must act immediately and another drug must be long-acting. The applicant's argument that Conte teaches a third barrier layer that is drug-free and does not contain rate-controlling polymers is not persuasive since Conte also teaches an immediate release layer adjacent to a sustained release layer. Furthermore, the instant claims utilize "comprising" claim language and hence the use of additional components, asides from those recited is permitted in the claims. The applicants have not shown any unexpected results that accrue from the instant bilayered tablet. The prior art explicitly teaches a tablet formulation comprising a combination of carbidopa and levodopa formulations with immediate and sustained release rates and recognizes the treatment of Parkinson's Disease by employing formulations of carbidopa and levodopa as instantly claimed. Hence, the instant invention remains unpatentable over the prior art of record.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (703) 308-4429. The examiner can normally be reached on Monday through Friday from 7:00A.M. to 4:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns
December 05, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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